

After any sufficiently effective treatment the extent of clinical recovery depends on the amount of the cerebral tissue that is capable of recovery and that is not a function of the treatment but of the viable cerebral tissue. Similarly the period of clinical recovery is the time required for the recovery of such cerebral tissue as is capable of restored activity. The final results cannot vary between one effective method of treatment and another, provided the treatments themselves are innocuous and reasonably prompt in their actions, and if an effective treatment has once been given no greater or quicker improvement can possibly be obtained by a multiplication of therapies. The practical results that have been obtained are in general agreement with this conclusion.

Our only criterion for the permanence of cures is the serological reactions. After the disease is arrested these take time to become normal; if the cerebrospinal fluid is of the "inactive" type after three months, and normal, apart from the colloidal gold reaction, within two years, we may be satisfied. Such results are obtainable with penicillin as with malaria, and there seems no reason why they should not be as permanent. Though serological relapses must be watched for, they are likely to be few.

### Conclusions

As a result of my observations I draw the following tentative conclusions—and I emphasize that they are tentative because longer observation is necessary.

1. Penicillin is sufficient in most cases of neurosyphilis. Whether it is adequate for the more acute cases of general paralysis of the insane the experience by this series does not show.

2. If, with the possible exception of such cases, the patient can be kept under observation after treatment and penicillin repeated if necessary, malaria will seldom be called for, and the risk of it will seldom be justified.

3. Even if penicillin does not render malaria unnecessary, it is a potent weapon and will make us much less dependent on malaria, and risks which were necessary before need not now be taken.

I wish to express my thanks to Dr. J. N. Cumings for examination of the cerebrospinal fluids and bloods, and to Dr. J. S. Prichard for his help in following up the cases described.

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## DISCUSSION ON THE TREATMENT OF NEUROSYPHILIS WITH PENICILLIN

DR. W. D. NICOL said there was no doubt that malaria was not devoid of considerable risks. It was true that at Horton Hospital the mortality rate had been as high as 8 per cent.; nevertheless it was found that in the latent neurosyphilitic cases, of which quite a considerable number had now been treated, there was no mortality. Therefore it did appear with the patients in whom the more active process of disease was going on, as in general paralysis of the insane, that the risk was very much higher. It was quite clear that, for this most active disease process, treatment by malaria should be supplemented by something else, and at Horton Hospital they had based their conclusions on the work done with malaria and tryparsamide. He himself did not like tryparsamide, and Dr. Martin had not used it in any of the cases he had described that afternoon. How far penicillin might supersede malaria therapy remained to be seen. It would certainly entail very much less

clinical anxiety and trouble; but were they going to find that penicillin would be sufficient from the point of view of therapy? Dr. Martin, quite rightly, was cautious in his conclusions. They would have to wait several years to know the complete answer. Penicillin had been used to a considerable extent at Horton Hospital, where his colleague was getting together data on a hundred cases that had been under observation for one year and more.

He was glad to hear that Dr. Martin advocated confining oneself to one form of therapy and seeing what it would do before starting another. So far as optic atrophy or one of these major disasters was concerned, one had to be very quick about treatment and not waste time, but with other clinical manifestations one should be very careful to see what a particular form of therapy was capable of doing and what effect it was likely to have before abandoning it for something else.

He wished to ask, with regard to the first case of optic atrophy which Dr. Martin had described, why, if it did so well after 5 mega units of penicillin, it was necessary to give more. The dosage of penicillin, to judge from the literature, seemed to have settled down. He thought the optimum dosage the Americans gave varied from 4 to 6 mega units. At Horton Hospital they gave 4.2 mega units.

Was it really necessary to give penicillin 4-hourly over a period of days? At the malaria unit at Horton Hospital they gave one dose of 0.3 mega units daily for fourteen days. His impression was that the results compared favourably with Dr. Martin's, and if that were the case it would save trouble for both clinician and patient if the injections were given only once instead of three or four times a day.

In one paper from America a comparison was drawn between cases treated with malaria plus penicillin and cases treated with penicillin alone. In the combined therapy this worker reduced the number of peaks of fever with malaria from twelve to six, and the number of hours in the fever cabinet from 40 to 20. If they came to the conclusion that malaria should still remain in their armamentarium it was going to be of advantage to reduce the number of peaks of fever.

Was it necessary to worry about the blood Wassermann? He thought the important thing was to concentrate on the cerebrospinal fluid. He was certain that they had cases in which fifteen or twenty years had elapsed and in which a completely negative fluid had been obtained and yet the blood was still positive.

BRIG. T. E. OSMOND said he was inclined to agree with Dr. Nicol that it did not matter what the blood Wassermann was in late syphilis—anyway in general paralysis of the insane and tabes. Might he very humbly suggest that some of the pathological results recorded were a little suspect. He noticed that one case of G.P.I. gave a negative blood Wassermann shortly after a comparatively small amount of penicillin. That had not been his experience at all. In another case the Pandy test was negative but all the other tests were positive in the fluid and the blood. He thought this was an anomalous result.

With regard to the Herxheimer reaction, he was struck by the case of the woman who had 1 mega unit every day and, he gathered, had a reaction after every administration. That, again, had not been his experience.

DR. SUCHETT-KAYE quoted some cases of neurosyphilis treated at St. Charles's Hospital. The follow-up was not yet complete, but the results so far had been encouraging, though there had been a few inexplicable failures. Their impression was that the best results with penicillin were obtained in meningovascular syphilis, especially in the acuter forms. The immediate results were excellent with penicillin alone. All other anti-specific measures served to consolidate the results obtained.

A sample case was a man aged 42, admitted to hospital with sudden right hemiplegia. The blood Wassermann and Kahn tests were both strongly positive. The cerebrospinal fluid, which showed an appreciable increase in cell count and protein content, gave a paretic Lange and a strongly positive Wassermann reaction. Penicillin was given three-hourly until 5 mega units were administered. This was followed by bismuth and arsenic. Three months after the onset of the paralysis the patient walked out of hospital. Subsequent tests were not done

as the patient had moved to another district and had been lost sight of.

Failures had been encountered, especially in the parenchymatous form of neurosyphilis. One patient, a man of 53, with general paralysis of the insane and syphilitic aortitis, received three courses of penicillin, one of 2.4, the two others of 4.8 mega units each, with no obvious benefit. Clinically and serologically there was no change, and the latest inquiries had shown that the patient was confined in a mental hospital.

They were impressed with the specific effect of intramuscular penicillin on the lightning pains of tabes dorsalis. These pains, including other forms of tabetic crises, disappeared for about six months or longer after penicillin therapy. In some instances they recurred. Repeated courses of penicillin would then be necessary.

Dr. Harkness had a case of typical tabes with a two years' history of severe lightning pains. These incapacitated the patient completely. A course of arsenic was not helpful, but bismuth gave a remission of more than a month. He then tried penicillin, twice daily 0.3 mega units in ethyl oleate for five days. Four days after the completion of treatment the pains, which during treatment had been greatly aggravated, disappeared entirely and had not reappeared after one year's observation.

Dr. Suchett-Kaye gave details of other cases, including the following:

A man, aged 38 years, had primary syphilis in 1945 for which no treatment was given. A year later he was admitted to St. Charles's Hospital with nervous symptoms and changes in the cerebrospinal fluid suggesting meningovascular syphilis. There were also large, destructive, painless ulcerative lesions on the penis and left forearm. Histological examination of tissue from ulcers showed chronic granulomatous lesion with giant-cell systems. The blood Wassermann and Kahn tests were strongly positive.

The cerebrospinal fluid showed 50 mg. per 100 ml. total protein, a slight increase in globulin, and 50 lymphocytes per c.mm. The Lange reaction was 1223211000, and the Wassermann reaction strongly positive. A total of 2.4 mega units of penicillin was given by 3-hourly injections. This was followed by a course of arsenic and bismuth.

The syphilides healed within seventeen days after starting penicillin. Six weeks after admission the Wassermann and Kahn tests were strongly positive. The cerebrospinal fluid showed a total protein of 70 mg. per 100 ml., and 12 lymphocytes per c.mm. The Lange reaction was 1222321000.

The patient was seen on Jan. 23 this year. His general condition remained excellent. He was then a cheerful man, 18 stone in weight. Typical old syphilitic scars were present. The Wassermann reaction was by then negative and the Kahn test doubtfully positive. His cerebrospinal fluid showed normal protein, and 1 cell per c.mm. The results of Lange and Wassermann reactions were not available.

SURGEON-COMMANDER MAGUIRE, R.N., said that in the Royal Navy the great difficulty in carrying out any investigation was to follow up the cases over an adequate period, and now their task had been made more difficult owing to the demobilization of a very high percentage of their patients. An effort was being made to follow the cases into civil life and to obtain details of progress from the civil clinics.

Surgeon-Commander Maguire had examined the records of approximately 6,000 cases of syphilis treated

with penicillin during 1945-7. The majority of these were fresh infections in the primary and secondary stages and the remainder were "latent" or congenital cases. Routine cerebrospinal investigations were carried out in 2,062 of the 6,000 cases (approximately 34 per cent.) usually in the third or fourth month after the commencement of treatment; many cases had more than one investigation. Of the 2,062, 1,932 (93.6 per cent.) were completely normal; 130 (6.4 per cent.) showed some abnormality, but none of these had any clinical signs of nervous involvement. An attempt was made, with the following result, to divide the abnormals into the three grades suggested by Earle Moore:

Abnormal C.S.F.	% approx.	Grade
23	17.6	I. Increase of cells only.
15	11.5	II. Increased cells and protein, with variable gold curve and weak positive W.R.
24	18.6	III. Increased cells and protein, paretic curve, and positive W.R.
6	5.3	Between grades II and III.
62	47.7	Would not fit into any of the grades but had variable combinations of all three.

Of the 45 cases with the more gross changes (Grades II and III), 20 gave no history of previous venereal disease. All had been treated with penicillin, and during the past fifteen months arsenic and bismuth had also been given.

The records of 30 cases of symptomatic neurosyphilis treated at one of the Naval mental hospitals were also examined. These consisted of general paralysis of the insane (14), tabo-paresis (8), tabes (2), cerebral (4), and menigovascular (2). Of the 14 cases of G.P.I., 5 had no previous history of venereal disease and 2 had had malaria during service abroad. Of the 8 tabo-paretics, 4 had no previous history and one had had malaria. Nineteen of the cases suffering from G.P.I. and tabo-paresis were treated with single daily doses of penicillin given intravenously (0.3 to 0.5 mega units for 10 to 14 days) and 8 also had malaria or arsenic or both. Physical improvement was noted in 15 of the 19. In several of the cases of G.P.I. investigated 6 to 12 months later the cerebrospinal fluid had returned to normal. It could not be said at this stage whether the improvement was maintained, as all these cases were invalided out of the Navy.

DR. DAVID NABARRO said that if penicillin fulfilled the promise held out before them it would be a great advance in the treatment of these cases. He did not think other neurologists were all in agreement with Dr. Martin. Some of them said they could not quite make out how penicillin could reach the parasites in the substance of the brain, and they still thought penicillin should be supplemented by some of the older methods of treatment.

As Dr. Martin had admitted, the time that had elapsed since the treatment had been completed was not sufficiently long for him or any of us to be certain that

the cure was going to be permanent. Time was necessary before it could be said that any particular drug or form of treatment was an effective "cure."

In this connexion he thought it might be of interest if he recorded a few of his cases in which adequate time for the assessment of cure had elapsed. In 1925 a girl aged 6 years was admitted to the Hospital for Sick Children, Great Ormond Street, London, on account of loss of memory and strange behaviour. She was under the care of Dr. (now Sir) Robert Hutchison, and as shortly after admission she became maniacal and showed the characteristic blood and cerebrospinal fluid changes of general paralysis of the insane she was transferred to his (Dr. Nabarro's) ward for treatment. The onset having been acute, according to the mother—though it later transpired that the child's schoolteacher had noted a change in her mental condition for several months past—he thought this might be regarded as a test case, so after the least possible delay treatment was begun. This consisted of mercury iodide, neoarsphenamine, bismuth, bistovol, and a course of malaria between two courses of intracisternal injections of salvarsanized serum—the last-named line of treatment he had seen effectively used by Sir James Purves-Stewart in several cases of general paralysis of the insane. Owing to the patient's acute mental condition she was hardly suitable for treatment in a children's hospital—even in a small special ward—but as she appeared to be a "test" case and as the ward Sister was very keen to co-operate, treatment on the lines outlined above was continued for more than two years, with the result that the child became apparently normal, though somewhat backward mentally, and her blood and cerebrospinal fluid became negative and normal in all respects and have remained so ever since. She was now 28 years of age but her mentality was that of a child of 5 or 6, the age at which she had been smitten by the G.P.I., and on that account he had regarded the case as a failure although her specific disease had been cured. That week he had heard from the medical superintendent of the institution where the patient was an inmate to the effect that she was able to do simple work in the institution laundry and proved quite useful.

He recalled two men whom he had treated similarly with neoarsphenamine, intracisternal injections of salvarsanized serum, malaria, mercury, and bismuth. One was a man, aged 44, who had tabo-paresis and lived for fifteen years, though latterly with a Charcot arthropathy. His Lange test became nearly normal after one year's treatment and did not relapse in nine subsequent tests. The other patient died last year at the age of 66, twenty-five years after he had been diagnosed as a general paretic for which he had been "certified." During most of those 25 years he led an active and useful life, "decertified."

Treatment by the intracisternal injection of salvarsanized serum had not been much practised in this country, for the reason—he supposed—that it was a difficult and rather laborious line of treatment. He had achieved better results in his cases of congenital neurosyphilis with the combined treatment than with either separately. These cases he thought might be of interest to the Society owing to the number of years, 15, 25, and 22, that the patients survived.

He did not share the opinion which had been expressed that no serious attention need be paid to sero-resistance. In his opinion when a patient was suffering, or had suffered, from clinical neurosyphilis, every effort, including the application of fever therapy, should be made to obtain the reversal of the blood Wassermann reaction. A persistent positive reaction must mean, he

thought, persistence of the treponemes in the body with the possibility of a relapse of the neurosyphilis. He had seen this happen to several of his patients with congenital syphilis.

DR. DOUGLAS CAMPBELL said that during last year he had had to deal with several cases of general paralysis of the insane, and he wished to make one brief point which had not been substantiated long enough to permit him to speak positively, although it was interesting. The use of penicillin as a preparatory drug before going on to malaria did seem to have considerable benefit. That, indeed, was borne out by Dr. Martin's paper. But to achieve the social improvement necessary to keep the patient out of a mental home he thought that the subsequent use, within two or three weeks, of malaria was particularly beneficial.

DR. ROBERT LEES said that warning was necessary against the precipitate use of penicillin in patients with neurosyphilis who also had cardiovascular lesions. Some patients became much worse, and this could probably be prevented by an adequate period of preliminary treatment with bismuth and iodides.

He had deliberately adopted a technique of treatment of *tabes dorsalis* and general paralysis of the insane which combined fever therapy (malaria) and penicillin. About forty cases had now been treated without a death, as a relatively short malaria course was advised. The penicillin was originally given in doses of 5 to 10 mega units during the incubation period of the malaria. Recently the penicillin was given during the fever. He adopted this combined therapy on account of doubts prompted by failures of penicillin to cure early syphilis. The patients were usually observed for six months after fever therapy without any additional treatment, but if clinical or serological results were not satisfactory he gave tryparsamide and bismuth, or in a few paretics repeated the penicillin and fever therapy.

Results in early G.P.I. were very good, but in juvenile (congenital) cases they were disappointing.

In *tabes dorsalis* his experience had not been so fortunate as that of some of the speakers. About half the cases had very marked relief of symptoms after penicillin, but in some this only lasted for about a year. In a few tabetics there was a spectacular remission of symptoms with physical improvement. Some of the patients had severe aggravation of their symptoms during the penicillin administration.

DR. D. I. WILLIAMS said that they all knew that in cases of early syphilis treated with penicillin they got a proportion of failures. This proportion varied with different treatments. Often it was as high as 25 per cent. Probably, therefore, they must expect in the later stages of syphilis that the proportion of failures would be as great or greater. He felt strongly that penicillin, apart from its value without ancillary treatment, should be

supplemented by fever. During the whole afternoon's discussion, fever had been discussed in the terms of malaria only. But artificial fever he still thought to be safer. One could induce artificial fever for as long as one wanted, as often as one liked, and as high as was desired, and one could stop it any time. He considered that there would be less danger in using penicillin with artificial fever than in using it with malaria.

The discussion had demonstrated the fact that each of them could produce a small handful of cases, but because of the paucity of the number of cases no conclusive evidence could be drawn. What was wanted was a large series of cases treated in the same way. The time had come when some common routine of treatment should be agreed upon. Of course no clinician would or could be compelled to use a given form of treatment, but those who were willing might meet together and discuss what they would like to do and thereafter carry out one particular line of treatment; thus more satisfactory evidence would be forthcoming. As it was they could gather only mass individual impressions such as had been heard during the present discussion.

DR. PURDON MARTIN, in reply, said it was very evident from the discussion that they all had the same difficulties. This was a new method of treatment, and they did not know where they were. He thought he did emphasize in his paper that one's attitude must be determined by one's feeling towards malaria and one's experiences with it. They had not had any big series, and from the figures he had quoted it appeared that the results obtained clinically with three different forms of antisypilitic treatment were all very much alike. What they had to determine with regard to penicillin was whether it was an effective treatment, that is, whether it was a method which could kill the disease, and whether, if it was effective, it was likely to do any harm to the brain. If these questions were answered favourably they were obviously going to get quite as good clinical results with penicillin alone as with malaria.

Again, they were up against the difficulty of having to wait for the clinical improvement. The results in these cases were not obtained immediately, they had to be waited for. Knowing that they were dealing with such a condition as general paralysis of the insane, had they the courage to wait after giving a patient penicillin, and not go on at once to give him malaria? As a result of his experience he urged them to give penicillin alone and then wait, provided the clinical condition of the patient was satisfactory. It was only in that way that they would be able to determine its value.

In regard to the method of administration of penicillin, that was still *sub judice* and they had still to find the optimum technique. Various techniques were being developed which had the effect of keeping up the concentration of penicillin in the blood by reducing the rate of excretion, and possibly one of these would eventually make the treatment more convenient.